

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number**      **20-869**

**CHEMISTRY REVIEW(S)**

# Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

## Review of Chemistry, Manufacturing, and Controls

<b>NDA #:</b> 20-869	<b>REVIEW #1</b>	<b>DATE REVIEWED:</b> February 3, 1998
<b>SUBMISSION TYPE</b>	<b>DOCUMENT DATE:</b>	<b>ASSIGNED DATE</b> <b>USER FEE DATE</b>
Original submission	6-25-97	7-01-97 6-25-98
Amendment 1	8/1/97	(To provide CFN No for a manufacturing facility)
Amendment 2	8/21/97	(To provide a revised page C-13)
Amendment 3	9/17/97	(To provide request for Categorical Exclusion for EA)
Amendment 4	9/24/97	(To provide a new timolol maleate assay method)
Amendment 5	10/17/97	(To provide fill volumes and capacities of the marketing containers/closure systems)
Amendment 6	10/23/97	(to provide correction of the submission)
Amendment 7	12/19/97	(to provide site specific stability data)

Being reviewed: All above.

**NAME & ADDRESS OF APPLICANT:** Merck & Co. Inc., BLA-30, West Point PA 19486

### DRUG PRODUCT NAME

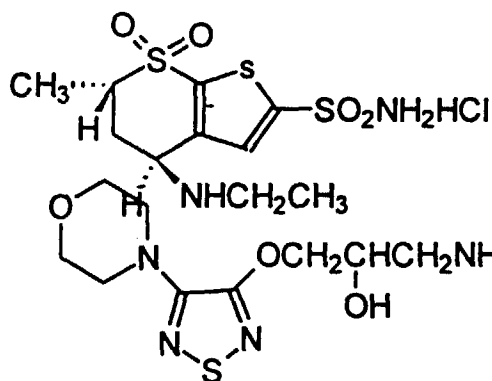
Proprietary: Cosopt

Established: Dorzolamide HCl and Timolol Maleate

Code Name/#:

Chem. Type/Ther. Class: A non-selective adrenergic receptor blocking agent which, when applied to the eye, reduces elevated as well as normal intraocular pressure (IOP).

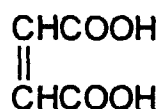
### CHEMICAL STRUCTURE:



Dorzolamide HCl

Formular  $C_{10}H_{16}N_2O_4S_3 \cdot HCl$

M. W. 360.91



Timolol Maleate

$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

**PHARMACOL. CATEGORY:** Ophthalmic Solution

**DOSAGE FORM:** Ophthalmic Solution

**STRENGTHS:** 2.0%/0.5%

**ROUTE OF ADMINISTRATION:** Ophthalmic

**DISPENSED:** ☒ Rx ☐ OTC

**COMMENTS:** The submission is deficient but approvable. See review for details.

**REMARKS:**

1. DMF status: Satisfactory.

No review is necessary. Information related to dorzolamide drug substance was referenced to Merck's approved NDA 20-408. Drug substance timolol maleate was referenced to Merck's approved NDA 18-086. Merck stated that an agreement was reached with the agency in the pre-NDA filing meeting that no additional information was needed in support of the submission of this NDA.

2. Consultation review status:

- a. Nomenclature Committee has reviewed the proposed propriety name and found the name "COSOPT" acceptable. A copy of the request is attached to this review.
- b. The review of the submissions related to microbiology sent to the microbiologist in HFD-160 has been complete. The submission was found approvable. A copy of the review is attached to this review.

3. EER status: cGMP inspection of the firms found that the facilities were all acceptable. a copy of the acceptable EER is attached.

4. Container/Closure (C/C) system:

- a. Container:

Drug product will be dispensed as 5 mL and 10 mL solutions.

b. Tip:

C. Label:

5. Method validation: Copies of the method validation packages were sent to Philadelphia District lab and St. Louis Lab dated 7/15/97 for validation.
6. Expiration dating period: Requests 24 month expiration date.
7. Environmental Assessment: Requests for Categorical exclusion.

**CONCLUSION OF THE REVIEW:** Approvable with comments. See comments at the end of the review.

Bart Ho, Review Chemist

Team Leader, Hasmukh Patel

2598

cc:

Orig. NDA 20-869 -  
HFD-550/Division File  
HFD-550/BHo  
HFD-550/Gorski  
HFD-830/Chen

**Filename:** N20869R1.BHo

**APPEARS THIS WAY  
ON ORIGINAL**

# Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

## Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-869      **REVIEW #2**      **DATE REVIEWED:** March 16, 1998

**SUBMISSION TYPE**      **DOCUMENT DATE:**      **ASSIGNED DATE**      **USER FEE DATE**

Original submission	6-25-97	7-01-97	6-25-98
Amendment 1	8/1/97 (To provide CFN No for a manufacturing facility)		
Amendment 2	8/21/97 (To provide a revised page C-13)		
Amendment 3	9/17/97 (To provide request for Categorical Exclusion for EA)		
Amendment 4	9/24/97 (To provide a new timolol maleate assay method)		
Amendment 5	10/17/97 (To provide fill volumes and capacities of the marketing containers/closure systems)		
Amendment 6	10/23/97 (to provide correction of the submission)		
Amendment 7	12/19/97 (to provide site specific stability data)		
Amendment 8	2/28/98 (to provide response to review chemist comments)		

**Being reviewed:**      Amendment #8

**NAME & ADDRESS OF APPLICANT:** Merck & Co. Inc., BLA-30, West Point PA 19486

**DRUG PRODUCT NAME**

Proprietary: Cosopt

Established: Dorzolamide HCl and Timolol Maleate

Code Name/#:

Chem.Type/Ther.Class: A non-selective adrenergic receptor blocking agent which, when applied to the eye, reduces elevated as well as normal intraocular pressure (IOP).

**PHARMACOL. CATEGORY:** Ophthalmic Solution

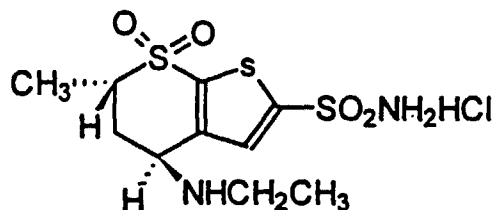
**DOSAGE FORM:** Ophthalmic Solution

**STRENGTHS:** 2.0%/0.5%

**ROUTE OF ADMINISTRATION:** Ophthalmic

**DISPENSED:**        X   Rx       OTC

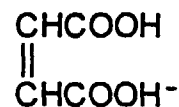
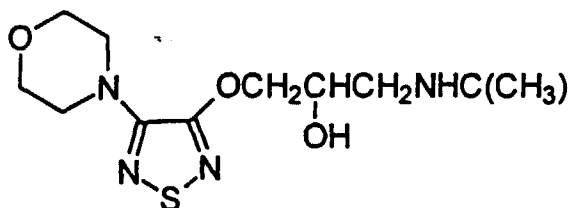
**COMMENTS:** The submission is complete. Recommend approve.

**CHEMICAL STRUCTURE:**

Dorzolamide HCl

Formular  $C_{10}H_{16}N_2O_4S_3 \cdot HCl$ 

M. W. 360.91



Timolol Maleate

 $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ 

432.50

**REMARKS:**

1. DMF status: Satisfactory.

No review is necessary. Information related to dorzolamide drug substance was referenced to Merck's approved NDA 20-408. Drug substance timolol maleate was referenced to Merck's approved NDA 18-086. Merck stated that an agreement was reached with the agency in the pre-NDA filing meeting that no additional information was needed in support of the submission of this NDA.

2. Consultation review status:

- a. Nomenclature Committee has reviewed the proposed propriety name and found the name "COSOPT" acceptable. A copy of the request is attached to the previous review.

- b. Submissions related to microbiology has been sent to the microbiologist in HFD-160 for review. The review currently is pending.
- 3. EER status: cGMP inspection of the firms found that the facilities were all acceptable. a copy of the acceptable EER is attached to the previous review.
- 4. Container/Closure (C/C) system:
  - a. Container:
  - b. Cap:
  - c. Tip:
  - d. Label:
- 5. Method validation: Method validation sent to Philadelphia District lab dated 7/15/97 has been complete. The method was deemed suitable for regulatory control of the drug product. A copy of the validation package is attached to this review.
- 6. Expiration dating period: Requests 24 month expiration date.
- 7. Environmental Assessment: Requests for Categorical exclusion.

**CONCLUSION OF THE REVIEW: Recommend Approve**

Bart Ho, Review Chemist

3/16/98

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Team Leader, Hasmukh Patel

3-17-98

cc:

Orig. NDA 20-869

HFD-550/Division File

HFD-550/BHo

HFD-550/Gorski

HFD-830/Chen

#FD-550/no/Chambers

**Filename:** N20869R2.ABH

**APPEARS THIS WAY  
ON ORIGINAL**